PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 444.83013000	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05659	International filing date *(day/month/year)* 22.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07H17/08, C07H17/00		
Applicant ALPHARMA APS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.07.2004	07.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bardili, W Telephone No. +49 89 2399-2132

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05659

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-104 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5, 10: in all respects; 8,9: with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 8, 9 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5, 10 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 6-9 (parts)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 6-9 (parts) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-9 (parts)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	6-9 (parts)
Industrial applicability (IA)	Yes:	Claims	6,7 (parts)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Clarity, coverage of the search:

Claims 1-5 do not clearly define the subject-matter for which protection is sought since in the absence of any clear definition of the type of macrolide in the claims the indication *10-substituted desmethyl* has not a distinct meaning. Furthermore, the expression desmethyl does not indicate which substituents replace the methyl group. Apparently, essential information as to the structure of the claimed compounds is not present in the claim language of claims 1-5.

Claim 10 is unclear for similar reasons.

Hence, the subject-matter of claims 1-5, and 10 is not examined in respect of novelty, inventive step, and industrial applicability.

2. The inventions 3 and 4 have not been searched since the applicants did not pay the additional search fees (see item IV below). Consequently, these inventions are not considered in this report.

3. Medical treatment of the human body:

Claims 8 and 9 relate to medical treatment of the human body and hence to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The application comprises four inventions:

Invention 1:
Claims 1-9 (parts): compounds as represented by formula (II), pharmaceutical compositions containing them and their use

Invention 2:
Claims 1-9 (parts): compounds as represented by formula (III), pharmaceutical compositions containing them and their use; and intermediates to prepare them according to claim 10

Invention 3:
Claims 1-9 (parts): compounds as represented by formula (IV), pharmaceutical compositions containing them and their use

Invention 4:
Claims 1-9 (parts): compounds as represented by formula (V), pharmaceutical compositions containing them and their use

(I) The application relates to a class of macrolide antibiotics which are described as *10-substituted-10-desmethyl macrolides*. The expression *10-substituted-10-desmethyl* appears to be related to a C13O lactone ring carrying further substituents (see definition at page 3 of the specification) although this is not mentioned in the claims. In the absence of any unambiguous definition of the type of macrolide in the claims the indication *10-substituted desmethyl* is given the indicated meaning.

The applicants found that in such ring systems the 10-methyl group is not necessary for the antibiotic activity and may be replaced with other substituents (see page 3). This appears to be the basic concept underlying the invention.

The international application WO-A-98 51 695 discloses macrolide antibiotics having a C13O-lactone ring which is modified at position 10, for instance by 10-ethyl (see claim 1; and table 1). Similar subject-matter is disclosed in WO-A-98 01 571, claims 1 and 29. The general concept underlying the application as indicated in the description is hence not new and cannot establish a single general inventive concept within the meaning of Rule 13.1 PCT.

(ii) The definition of the claimed compounds in claims 1-5 is incomplete since an essential part of the claimed compounds is not clearly defined by the expression "macrolide". Therefore, claim 6 comprising 4 Markush formula to define the claimed compounds is taken to examine which groups of inventions are contained in the application.

The formulae (II) to (V) do not comprise a common or special technical feature that makes a contribution over the prior art since, as correctly expressed in the description, the substitution pattern at the ring atoms beyond C-10 in the claimed compounds is conventional and has been suggested in over 50 years (see page 2 of the description and the review article "Recent developments in 14- and 15-membered macrolides" mentioned in the search report). In particular, the 3-keto modification, the optional 6-hydroxy-substitution, the 9-keto modifications and the 11,12-ring expansion are well-known in the art (see the mentioned review article, under the appropriate heading).

Consequently four independent inventions which are not linked by a single general inventive concept are contained in the application.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1:

WO-A-02 060 912 and in particular WO-A-98 01 571, claim 1, and WO-A-98 51 695, claim 1 and table 1, show that the 10-methyl group is not an essential requirements for C13O macrolides and in particular erythromycins of formula II to be active antibacterial agents. When wishing to provide new antibacterials a skilled person would therefore have considered replacing 10-methyl with 10-ethyl or another substituent. The claimed subject-matter is hence obvious.

Invention 2:

FR-A-2 692 579 and WO-A-98 51 695, claim 1 and table 1, show that the 10-methyl group is not an essential requirements for C13O macrolides and in particular erythromycins of

formula III to be active antibacterial agents. When wishing to provide new antibacterials a skilled person would therefore have considered replacing 10-methyl with 10-ethyl or another substituent. The claimed subject-matter is hence obvious.

Invention 1 and 2:

For the assessment of the present claims 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.